This book provides very good understanding to undergraduate students. Elaborated clinical cases are included. It is a more clinically oriented book than other Biochemistry book. New topics which are essential, are also covered very well.

Dr. Ghuge Ganesh D Professor & Head
VPMC Hospital and Research center Adgaon, Nasik

Review of questions given helps for entrance exam also, it is nice to give for each topic. In some topics like lipids more explanation may not be needed. This book is as per syllabus, also contains MCQs which doesn’t make us to refer extra MCQs Books. Almost every topics has been covered and all topics are in good sequence. This books gives Simplified, easily understandable, elaborating topic in a good manner.

Mr. Abhishek
Dr. B.R. Ambedkar Medical College
Bangalore

Recommended to all 1st year Medical students. In addition to this text book, I received a Revision Book, which contains essay questions, Short notes, Viva-Vice and MCQ questions.

Dr. VP Suryakar Assistant Professor
Dept of Biochemistry MVPS Dr. V.P.M.C. Adgaon, Nashik

Good book with full colour diagrams with additional booklet contains Q & A.

Dr. SN Jangle Professor & Head
Dept. & Biochemistry, Rural Medical College, Loni, Ahemdnagar

Satisfied in all aspects including content, delivery, packing, cost

Dr. Jaskiran Kaur
Ass. Professor, Biochemistry Subharti Medical College Meerut, Uttar Pradesh

How this Book is Useful?

Features
- Comprises concise contents aimed at under-graduate students. The seventh edition contained a few extra paragraphs in each chapter, meant for post-graduate students. These extra portions are removed from the eight edition, so that the book is very helpful for undergraduate students.
- As per syllabus recommended by the Medical Council of India
- Relevant clinical correlations are given in respective chapters
- Cross-references given in all chapters for text, figures and tables for ease of understanding
- More than 1000 figures, 200 tables and 200 boxes. This is an illustrated textbook of biochemistry
- Figures are presented with precise and lucid manner
- A total of 100 clinical case studies are offered at the end of relevant chapters
- Each chapter is starting with “Chapter at a glance” and ending with “Learning Points”

- At the end of each chapter, a few MCOs, short questions, essays and viva voce questions are added, for easy revision of that chapter.
- Normal laboratory values are accessible in the appendix.
- Concise index is available to facilitate subject searches
- Relevant advanced content included to stimulate active learning for above-average students.
- Textbook is divided into sections for capturing the contents and contents are conveniently organized into small 50 chapters
- Large font size for easy reading
- High quality paper for less eye strain
- History of scientific achievements are shown for motivating the learner
- Pictures of scientists are attached to inspire the readers
- More than 1,50,000 copies are sold, including all editions
- Spanish and Slovak editions are available
- Accepted as a standard textbook in more than 30 countries
Preface to the Eighth Edition

We are glad to present the Eighth edition of the *Textbook of Biochemistry for Medical Students*. Now, this Textbook is entering the 22nd year of existence. With humility, we may state that the medical community of India has warmly received the previous editions of this book. The Medical Council of India have accepted it as one of the standard textbooks. We are happy to note that this book has also reached in the hands of medical students of neighboring countries of Nepal, Pakistan, Bangladesh, Sri Lanka, etc., and also to distant countries in Africa and Europe. We are very proud to report that the Textbook has a Spanish edition, with wide circulation in the Central and South America. Slovak edition has also been published. Apart from the medical community, this book has also become popular to other biology group of students in India. In retrospect, it gives immense satisfaction to note that this textbook served the students and faculty for the past more than two decades.

From the first edition onwards, our policy was to provide not only basic essentials, but also some of the advanced knowledge. About 30% contents of the previous editions were not required for an average student aiming for a pass. A lot of students have appreciated this approach, as it helped them to pass the PG entrance examinations at a later stage. However, this asset has paved the way for a general criticism that the extra details are a burden to the average students. Especially when reading for the first time, the students may find it difficult to sort out the essential minimum from the advanced portions. We have accepted the request from the majority of the students, and reduced the content in this edition.

Thus, in consultation with the Publishers, we have decided to make two different books, one for MBBS and another one for postgraduate courses in Biochemistry. Thus, the content has been made lesser in this textbook. We are bringing out the postgraduate textbook in due course.

Yet another regular criticism against the previous edition was that the font size was small, and it was difficult to read the book. This problem is solved in this edition, by changing the font. The readability has thus been markedly improved. While increasing the font size, we were very conscious that the bulk of the book should not be increased. We have reached a compromise in these mutually opposing tasks.

A major attraction of this edition is the incorporation of clinical case studies in almost all chapters. We hope that this feature will help the students to identify the clinical relevance of the biochemistry. Further, clinically relevant points were added in most of the chapters. Rapid progress has been made in the area of molecular biology during past few years, and these advances are to be reflected in this book also.

Essay questions, short notes, multiple choice questions and viva voce type questions are given at the end of almost every chapter. These questions are compiled from the question papers of various universities during the last decade. These questions will be ideal for students for last-minute preparation for examinations.

A textbook will be matured only by successive revisions. In the preface for the first edition, we expressed our desire to revise the textbook every 3 years. We were fortunate to keep that promise. This book has undergone metamorphosis during each edition. Chemical structures with computer technology were introduced in the second edition. Color printing has been launched in the third edition. The fourth edition came out with multicolor printing. In the fifth edition, the facts were presented in small paragraphs, so as to aid memory. In this sixth edition, figures were drastically increased. In the seventh edition, about 100 cases studies were added. In this 8th edition, extra topics have been pruned out. But the figures and boxes have been increased. Thus there are about 1000 figures, 200 tables and 200 boxes, altogether making the book more student-friendly. The quality of paper is also improved during successive editions.

We were pleasantly surprised to receive many letters giving constructive criticisms and positive suggestions to improve the textbook. These responses were from all parts of the country (we got a few such letters from African and European students also). Such contributors include Heads of Departments, very senior professors, middle level teachers and mostly postgraduate students. We have tried to incorporate most of those suggestions within the constraints of page limitations. In a way, this book thus became multiauthored, and truly
national in character. This is to place on record, our deep gratitude for all those “pen-friends” who have helped us to improve this book. The first author desires more interaction with faculty and students who are using this textbook. All are welcome to communicate at his e-mail address <dmvasudevan@yahoo.co.in>

As indicated in the last edition, the first author is in the process of retirement and would like to reduce the burden in due course. A successful textbook is something like a growing institution; individuals may come and go, but the institution will march ahead. The third author has been co-opted in the sixth edition. In the seventh edition, the third author took about 10% of the editing work. In this eighth edition, he was responsible to do almost 50% of the editorial work. Accordingly, the first and second authors have taken less pain in editing the book. Thus gradually, the torch is being handed over smoothly to the next generation; and that process will continue in the next editions.

The help and assistance rendered by our postgraduate students in preparing this book are enormous. The official website of Nobel Academy has been used for pictures and biographies of Nobel laureates. Web pictures without copyright protection were also used in some figures. The remarkable success of the book was due to the active support of the publishers. This is to record our appreciation for the co-operation extended by Mr JP Vij, and his associates.

We hope that this eighth edition will be friendlier to the students and be more attractive to the teachers. Now this is in your hands to judge.

“End of all knowledge must be building up of character”.

Mahatma Gandhi

May 2016

DM Vasudevan MBBS MD FAMS FRCPath
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CLINICAL SIGNIFICANCE OF CHOLESTEROL

Students should be familiar with cholesterol and lipoproteins described in detail in Chapter 14. A summary of lipoproteins is given in Table 15.1 and their metabolic relationships are shown in Figure 15.1. LDL is said to be “bad” cholesterol and HDL is “good” cholesterol (Fig. 15.2). High cholesterol levels are associated with atherosclerosis. Abnormality of cholesterol metabolism may lead to cardiovascular accidents and heart attacks.

ATHEROSCLEROSIS

Greek word, sclerosis means hardening. Coronary artery obstruction and myocardial infarction top the list of killer diseases in the world. In India 20% deaths are due to coronary artery disease (CAD). It is estimated that by the year 2020, it will account for 33% of all deaths.

Atherosclerosis and LDL

Stage I: Formation of Foam Cells

Increased levels of cholesterol for prolonged periods will favor deposits in the subintimal region of arteries. Aorta, coronary arteries and cerebral vessels are predominantly affected by the atherosclerotic process. The LDL cholesterol, especially oxidized LDL particles are deposited in the walls of arteries. Plasma LDL is mainly catabolized via apo-B-LDL receptor pathway. But a small part of LDL particles are degraded by nonspecific uptake by macrophages. Free radical induced oxidative damage of LDL will accelerate this process. Later, the macrophages become overloaded with cholesterol, and

TABLE 15.1: Characteristics of different classes of lipoproteins

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>Chylomicron</th>
<th>VLDL</th>
<th>LDL</th>
<th>HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density g/L</td>
<td>&lt;0.95</td>
<td>0.95–1.006</td>
<td>1.019–1.063</td>
<td>1.063–1.121</td>
</tr>
<tr>
<td>Diameter (nm)</td>
<td>500</td>
<td>70</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>Electrophoretic mobility</td>
<td>origin</td>
<td>pre-beta</td>
<td>beta</td>
<td>alpha</td>
</tr>
<tr>
<td>Apoproteins</td>
<td>A, B-48, C-II, E</td>
<td>B-100, C-II, E</td>
<td>B-100</td>
<td>A-I, C, E</td>
</tr>
<tr>
<td>Transport function</td>
<td>TAG from gut to muscle and adipose tissue</td>
<td>TAG from liver to muscle</td>
<td>Cholesterol from liver to peripheral tissues</td>
<td>Cholesterol from peripheral tissues to liver</td>
</tr>
</tbody>
</table>
Stage II: Progression of Atherosclerosis

Smooth muscle cells containing lipid droplets are seen in the lesion. During early stages of atherosclerosis, the condition is reversible if plasma lipid levels, especially LDL-cholesterol levels are lowered. But when lipid accumulates, the lesion progresses unchecked and the arterial changes become irreversible.

Stage III: Fibrous Proliferation

Due to liberation of various growth factors by macrophages and platelets collagen is accumulated. Thus there is a definite component of inflammation in atherosclerosis. This chronic infection leads to increased plasma high sensitive C-reactive protein (hs-CRP).

Stage IV: Advancing Fibrous Plaque

This leads to narrowing of vessel wall when proliferative changes occur (Fig. 15.3). The blood flow through the narrow lumen is more turbulent and there is tendency for clot formation.

Myocardial Infarction (MI)

Finally, a clot is formed which occludes one of the major vessels. Thrombosis in coronary artery leads to ischemia of the tissue supplied, due to hindrance to oxygen supply (Fig. 15.3). Ultimately infarction (death of tissue) occurs (Fig. 15.4). Result is inefficient contraction of heart muscle, and if allowed to progress further, death of the muscle cells in the affected region. Usually the diagnosis can be made from the clinical history, the electrocardiogram and cardiac markers (troponin T, CK-MB, etc, described in Chapter 6). Size of the infarct may be reduced by immediate administration of tissue plasminogen activator (t-PA).
PLASMA LIPID PROFILE

The sample of serum should be taken after 12 hours of fasting. A complete lipid profile is assessed by estimating the following parameters in plasma/serum.

1. Total cholesterol
2. HDL-cholesterol
3. LDL-cholesterol
4. Triglycerides
5. Apo-B level
6. Apo-A-I level
7. Lp(a) level

In routine clinical practice only the first four parameters are measured in a fasting sample.

Box 15.1 shows the conditions in which abnormal levels of serum cholesterol are seen. Box 15.2 gives the indications for checking the lipid profile.

RISK FACTORS FORATHEROSCLEROSIS

Risk factors for atherosclerosis and future myocardial infarction (MI) are shown in Box 15.3. Out of these, the total cholesterol, HDL and LDL levels are the most important indices (Box 15.4, item A). Cardiac markers, which indicate the presence of acute myocardial infarction are listed in Box 15.4, item B.

Serum Cholesterol Level

Framingham epidemiological study demonstrated that increase in serum cholesterol level is associated with increased risk of death from CHD. For every 10% lowering of cholesterol, CHD mortality was reduced by 13%. In healthy persons, cholesterol level varies from 150 to 200 mg/dL (Table 15.2). If other risk factors are present, cholesterol level should be kept preferably below 180 mg/dL. Values around 220 mg/dL will have moderate risk and values above 240 mg/dL will need active treatment. Females have a lower level of cholesterol which affords protection against atherosclerosis. Plasma cholesterol levels would tend to slowly rise after the 4th decade of life in men and postmenopausal women.

LDL-Cholesterol Level

National Cholesterol Education Program (NCEP) identified elevated LDL-C as a primary risk factor for CHD. Blood levels less than 130 mg/dL are desirable (Table 15.2). Levels between 130 and 159 are borderline; while above 160 mg/dL carry definite risk. Hence LDL is “bad” cholesterol (Fig. 15.2). Oxidized LDL initiates fatty streaks, which is the starting point of atheroma formation.
Chapter 15: Hyperlipidemias and Cardiovascular Diseases

**Non-HDL Cholesterol**

A value of more than 160 mg/dL carries high risk (Box 15.5).

**High Sensitive C Reactive Protein (hsCRP)**

It is also called ultra sensitive CRP. It measures low levels of CRP (1–10 ng/dL). It is a marker for risk for atherosclerosis and is used as a predictor for future myocardial infarction within the next 12 months. The hsCRP test clearly adds to the predictive value.

- Less than 1 mg/L (0.1 mg/dL) is considered as low risk and single measurement is sufficient. Levels between 1–3 mg/L are borderline, indicating some risk. Levels more than 3 mg/L is having high risk for future MI, and will need active medical intervention. If the hsCRP value is more than 10 mg/L, it indicates significant acute phase reaction, and is not indicative of any cardiac pathology.

**HDL-Cholesterol Level**

The HDL level above 60 mg/dL protects against heart disease. (Table 15.2). Hence, HDL is “good” cholesterol. A level below 40 mg/dL increases the risk of CAD. For every 1 mg/dL drop in HDL, the risk of heart disease rises 3%. If the ratio of total cholesterol/HDL is more than 3.5, it is dangerous. Similarly, LDL: HDL ratio more than 2.5 is also detrimental.

**Apoprotein Levels and Ratios**

Apo-A-I is a measure of HDL-cholesterol (good) and apo-B measures LDL-cholesterol (bad). Ratio of Apo-B: Apo-A-I is the most reliable index. The ratio of 0.4 is very good; the ratio 1.4 has the highest risk of cardiovascular accidents.

**Lp(a)**

Lp(a) inhibits fibrinolysis. Levels more than 30 mg/dL increase the risk 3 times; and when increased Lp(a) is associated with increased LDL, the risk is increased 6 times. (See Lp(a) in Chapter 14). Nicotinic acid will reduce serum Lp(a) level.

**Serum Triglyceride**

Normal level is 50–150 mg/dL. Blood level more than 150 mg/dL is injurious to health.

**Diabetes Mellitus**

Cardiovascular disease is responsible for 80% of total mortality in diabetes. It is associated with an increase...
in LDL, high TAG and low HDL levels. In the absence of insulin, hormone-sensitive lipase is activated, more free fatty acids are formed, which are catabolized to produce acetyl-CoA. These cannot be readily utilized, as the availability of oxaloacetate is reduced and citric acid cycle is sluggish. So acetyl-CoA pool is increased, and it is channeled to cholesterol synthesis.

In diabetes, atherogenic LDL is increased while atheroprotective HDL is decreased. The glycation and oxidation of LDL will promote the uptake by macrophages. At the same time, the level of HDL in diabetic patients and those with metabolic syndrome is low. Glycation of Apo-A-I decreases its ability to stimulate LCAT, and thereby the esterification and efflux of cholesterol from the cells.

**Smoking**

Cigarette smoking is the most important modifiable risk factor for CAD (Box 15.3). Risk from smoking is dose-dependent; depends on the age at which the person started smoking and the number of cigarettes smoked per day. Smoking enhances oxidation of LDL, reduces HDL, increases CRP and augments aggregation and adhesion of platelets. Nicotine of cigarette will cause lipolysis and thereby increase acetyl-CoA and cholesterol synthesis. Nicotine also causes transient constriction of coronary and carotid arteries.

**Hypertension**

Systolic blood pressure more than 160 further increases the risk of CAD. An increase in 10 mm of BP will reduce life expectancy by 10 years. Increase of 5 mm Hg of diastolic pressure is associated with 34% increase in stroke risk.

**Obesity and Sedentary Lifestyle**

The classical description of Pickwick (in Pickwick papers) by Charles Dickens reminds of a person with high risk for CAD. People with “apple type” of obesity or truncal obesity are more prone to get myocardial infarction. A person is obese when BMI exceeds 27.8 kg/m² in men and 27.3 kg/m² in women. Obesity causes glucose intolerance, insulin resistance, hypertension and dyslipidemia.

Adipose tissue releases a large number of bioactive mediators that influence insulin resistance leading to endothelial dysfunction and atherosclerosis. A summary of adipose tissue function is given in Chapter 35.

**Prevention of Atherosclerosis**

Almost 90% of CAD is predictable, preventable and curable. Lifestyle changes are required, which include regular exercise, balanced diet, cessation of smoking, maintaining proper weight, control of hypertension, diabetes and dyslipidemia. The aim is to reduce total cholesterol below 180 mg/dL; to decrease LDL-cholesterol below 130 mg/dl and to keep HDL-cholesterol above 35 mg/dL (Box 15.6).

**Reduce Dietary Cholesterol**

Cholesterol in the diet should be kept less than 200 mg per day. Eggs and meat contain high cholesterol. One egg yolk contains about 500 mg of cholesterol (Fig. 15.5A). One double omelet increases the blood cholesterol, 15 mg more than the original level.

**Vegetable Oils and PUFA**

Vegetable oils (e.g. sunflower oil) and fish oils contain polyunsaturated fatty acids (PUFA). They are required for the esterification and final excretion of cholesterol. Omega-3 fatty acids from fish oils reduce LDL and decrease the risk of CAD. Recommended intake of omega-3 fatty acid (fish oils) is 1 g/day (EPA and DHA combined). Clinical studies have suggested that DHA, (docosahexenoic acid) and EPA, (eicosapentaenoic acid) lower triglycerides; slow the buildup of atherosclerotic plaques; as well as reduce the risk of heart attack.

**Moderation in Fat Intake**

The accepted standard is that about 20% of total calories may be obtained from fat, out of which about one-third from saturated, another one-third from monounsaturated
and the rest one-third from polyunsaturated fatty acids. The recommended daily allowance will be about **20–25 g of oils** and about 2–3 g of PUFA per day for a normal adult.

**Green Leafy Vegetables**

Due to their **high fiber content**, leafy vegetables will increase the motility of bowels and reduce reabsorption of bile salts (Fig. 15.6). Vegetables also contain plant sterols (**sitosterol**) which decrease the absorption of cholesterol. About 400 g/day of fruit and vegetables are desirable.

**Avoid Sucrose and Cigarette**

Cigarette smoking (Fig. 15.7) is the single most important modifiable risk factor for CAD (Box 15.3). Sucrose will raise plasma TAGs. High carbohydrate diet, especially sucrose, should be avoided by patients with hypercholesterolemia.

**Exercise**

Regular moderate exercise (30 min per day) will lower LDL (bad cholesterol) and raise HDL (good cholesterol) levels in blood. It will also reduce obesity. Individuals spending more than 2000 kcal/week in exercise are at a lower risk.

**Hypolipidemic Drugs**

i. **HMG-CoA reductase inhibitors** ("statins"): Atorvastatin and Simvastatin are popular drugs in this group. They are effective in reducing the cholesterol level and decreasing the incidence of CAD.

ii. **Bile acid binding resins** (Cholestyramine and Colestipol) decrease the reabsorption of bile acids.

iii. **Probucol** increases LDL catabolism and prevents accumulation of LDL in arterial walls. So more cholesterol will be converted to bile acids, thus reducing the cholesterol level.

iv. **Aspirin** is widely used to prevent thrombus formation, because of its anti-platelet activity (see Chapter 16).

v. Anti-oxidants such as **vitamin E** will minimize oxidation of LDL and so, atherosclerosis may be reduced.

vi. Plant derived products having cholesterol-lowering action are enumerated in Box 15.7. The guggul (resins) from the Mukul myrrh tree (**Commiphora Mukul**) has cholesterol lowering action.

**Avoid Trans Fatty Acids (TFA)**

Trans fatty acids (with double bonds having trans configuration) are formed during the partial hydrogenation of vegetable oils. They are widely used in food industry because of their long shelf-life. Trans fatty acids (TFA) are found to be more atherogenic than saturated fatty acids. It alters secretion and composition of apo-B100 containing lipoproteins (LDL and VLDL). It increases catabolism of apo-A-I, decreases HDL and increases LDL levels. Reducing the intake of TFA to 2–7 g/day is now strongly advised.
PUFA, in Excess, may be Harmful

PUFA can definitely reduce cholesterol level. But there should be moderation. It is known that the diet should contain correct type and quantity; the optimum ratio of omega-6 to omega-3 fatty acids is 4:1. Very high intake of omega-6 oils will cause lowering of HDL, elevation of plasma triglycerides, and will promote platelet aggregation. Vegetable oils (sunflower oil) containing PUFA are rich in omega-6 variety; while ghee and butter are low in omega-3. Omega-3 group is present in fish oils. Normal Indian diet consisting of cereals, pulses and vegetables provides “invisible oils”, which contains about 10 g of PUFA/ day (out of which about 2 g is omega-3 and the rest 8 g is omega-6). Further intake of omega-6 oils is unnecessary and may be harmful.

The optimal ratio for omega-6 to omega-3 in diet is 4:1. In an average Indian diet, this is about 30:1. In sunflower oil, this value is 160:1, and therefore, unnecessary addition of such vegetable oils will further deteriorate the condition. Although contains saturated fatty acids, coconut oil has the omega ratio 3:1, and therefore is superior to sunflower oil in this respect.

The general advice against the use of ghee and coconut oil needs re-evaluation. This misinformation arose, when long chain saturated fatty acids (LCSFA) were shown to increase cholesterol level. Since butter and coconut oil also contain saturated fatty acids, people equated them with LCSFA. Now it is known that ghee and coconut oil contain small chain (SCFA) and medium chain fatty acids. The drastic differences in metabolisms of LCFA and SCFA are given in Chapter 16. In summary, ghee and coconut oil, within normal limits, neither decrease nor increase cholesterol levels. But it is to be noted that consumption of ghee (any oil in general), increases the total fat intake as well as calorie intake. That is harmful. Again, moderation is the key.

### HYPOLIPOPROTEINEMIAS

#### Abetalipoproteinemia

All apo-B containing lipoproteins are reduced since microsomal triglyceride transfer protein is defective. Hence TAG is not incorporated into VLDL and chylomicrons. (Table 15.3). Beta lipoprotein (LDL) is absent. Fat-soluble vitamins are not absorbed, causing mental and physical retardation. Serum levels of triglycerides, cholesterol and phospholipids are extremely low. Blindness may occur as a result of degenerative changes in retina. Erythrocytes have spiny projections (acanthocytes).

#### Hypoalphalipoproteinemia

This is inherited as an autosomal dominant trait. Serum HDL is decreased. There is increased risk for coronary artery disease (Table 15.3).

#### Tangier Disease

It was first described in patients from Tangier island in North-West Africa. It is a relatively benign, autosomal dominant condition. It is characterized by a defect in the efflux (flowing out) of cholesterol from cells, and reduction of HDL levels in the blood. The biochemical defect is the absence of “ATP-Binding Cassette Transporter-1” (ABC-1), which is involved in transferring cellular cholesterol to HDL. So, plasma HDL is low and alpha band is not seen in electrophoresis. Cholesterol esters are accumulated in tissues. Manifestations are large orange yellow tonsils, muscle atrophy, recurrent peripheral neuropathies and atherosclerosis.

### HYPERLIPIDEMIAS

The most widely accepted Fredrickson’s classification is shown in Table 15.4. In all cases of hyperlipidemias,
Chapter 15: Hyperlipidemias and Cardiovascular Diseases

The elevated lipid fraction is either cholesterol or TAG or both.

The elevation of lipids in plasma leads to the deposition of cholesterol on the arterial walls, leading to atherosclerosis. (See under coronary artery diseases). The coronary and cerebral vessels are more commonly affected. Thromboembolic episodes in these vessels lead to ischemic heart disease and cerebrovascular accidents.

The deposition of lipids in subcutaneous tissue leads to xanthomas. The type of xanthoma depends on the nature of lipid deposited. Eruptive xanthomata are small yellow nodules associated with deposition of triglycerides. They disappear when the lipid level falls.

Hyperlipidemias, in the order of highest to lowest incidence are Type IIA, IIB, IV, I, III and V.

Type IIA (Primary Familial Hypercholesterolemia)

There is elevation of LDL. Patients seldom survive the second decade of life due to ischemic heart disease (Table 15.4 and Fig. 15.8). The cause is LDL receptor defect. Receptor deficiency in liver and peripheral tissues will result in the elevation of LDL levels in plasma, leading to hypercholesterolemia. The LDL receptor defect may be due to the following reasons.

1. LDL receptor deficiency.
2. Defective binding of B-100 to the LDL receptors.

This defect is known as B-3500 or familial defective apo B.

3. Receptor-LDL complex is not internalized.

Secondary type II hyperlipoproteinemia is seen in hypothyroidism, diabetes mellitus, nephrotic syndrome and cholestasis (Table 15.5).

Salient features of other types of hyperlipoproteinemias are shown in Table 15.4. A summary of clinical classification of hyperlipidemias is shown in Box 15.8.

<table>
<thead>
<tr>
<th>Type</th>
<th>Lipoprotein fraction elevated</th>
<th>Cholesterol level</th>
<th>TAG level</th>
<th>Appearance of plasma after 24 hr</th>
<th>Metabolic defect</th>
<th>Features</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Chylomicrons</td>
<td>N</td>
<td>↑↑</td>
<td>Creamy layer over clear plasma</td>
<td>Lipoprotein lipase deficiency</td>
<td>Eruptive xanthoma; hepatomegaly; Pain abdomen.</td>
<td>Restriction of fat intake. Supplementation with medium chain triglycerides.</td>
</tr>
<tr>
<td>Type IIA</td>
<td>LDL</td>
<td>↑↑</td>
<td>N</td>
<td>Clear</td>
<td>LDL Receptor defect; Apo-B↑</td>
<td>Atherosclerosis, coronary artery disease, Tuberous xanthoma</td>
<td>Low cholesterol diet. Decreased intake of saturated fat. Give PUFA and drugs like statins.</td>
</tr>
<tr>
<td>Type IIB</td>
<td>LDL and VLDL</td>
<td>↑↑</td>
<td>↑</td>
<td>Slightly cloudy</td>
<td>Apo-B↑ Apo-CII</td>
<td>Corneal arcus</td>
<td>Do</td>
</tr>
<tr>
<td>Type III</td>
<td>Broad beta-VLDL and Chylomicrons</td>
<td>↑↑</td>
<td>↑</td>
<td>Cloudy</td>
<td>Abnormal apo-E; Apo-CII↑</td>
<td>Palmar xanthoma. High incidence of vascular disease</td>
<td>Reduction of weight, restriction of fat and chol. Give PUFA and drugs</td>
</tr>
<tr>
<td>Type IV</td>
<td>VLDL</td>
<td>↑</td>
<td>↑↑</td>
<td>Cloudy or Milky</td>
<td>Over-production of VLDL; Apo-CII↑</td>
<td>Associated with diabetes, heart disease, obesity.</td>
<td>Reduction of body weight. Restrict carbohydrate and cholesterol</td>
</tr>
<tr>
<td>Type V</td>
<td>VLDL Chylomicrons</td>
<td>N</td>
<td>↑↑</td>
<td>Creamy layer over milky plasma</td>
<td>Secondary to other causes</td>
<td>Chronic pancreatitis</td>
<td>High PUFA intake, hypolipidemic drug</td>
</tr>
</tbody>
</table>

Table 15.4: Fredrickson's classification of hyperlipoproteinemias (N = Normal; ↑ = Increased)

Fig. 15.8: Electrophoretic pattern of hyperlipidemias
Clinical Case Study 15.1
A 48-year-old male presents to the clinic because of concerns about heart disease. The patient reports chest pain occasionally with ambulation around his house and is not able to climb stairs without significant chest pain and shortness of breath. The physical examination is normal, and the physician orders an electrocardiogram (ECG), exercise stress test, and blood work. The patient’s cholesterol result comes back as 350 mg/dL (normal 200). The physician prescribes medication, which he states is directed at the rate-limiting step of cholesterol biosynthesis.

What is the rate-limiting step of cholesterol metabolism? What is the class of medication prescribed?

Clinical Case Study 15.2
A 51-year-old male presents to the emergency center with chest pain. He states that he has had chest discomfort or pressure intermittently over the last year especially with increased activity. He describes the chest pain as a pressure behind his breastbone that spreads to the left side of his neck. Unlike previous episodes, he was lying down, watching television. The chest pain lasted approximately 15 minutes and subsided on its own. He also noticed that he was nauseated and sweating during the pain episode. He has no medical problems that he is aware of and has not been to a physician for several years. On examination, he is in no acute distress with normal vital signs. His lungs were clear to auscultation bilaterally, and his heart had a regular rate and rhythm with no murmurs. An electrocardiogram (ECG) revealed ST segment elevation and peaked T waves in leads II, III, and aVF. Serum troponin I and T levels are elevated. What is the most likely diagnosis? What biochemical shuttle may be active to produce more adenosine triphosphate (ATP) per glucose molecule?

Clinical Case Study 15.3
A 48-year-old male presented to OP with chest pain. Family history shows that his father died of a heart attack at the age of 46, and his elder brother also had a heart attack at the same age. The patient reports that he gets chest pain occasionally with ambulation and is not able to climb stairs without significant chest pain and shortness of breath. His plasma cholesterol level was 450 mg%. What is the possible diagnosis?

Clinical Case Study 15.1 Answer
Diagnosis: Hypercholesterolemia.
Rate-limiting step: The enzyme hydroxymethylglutaryl-CoA reductase (HMG-CoA reductase) catalyzes an early rate-limiting step in cholesterol biosynthesis.
Likely medication: HMG-CoA reductase inhibitor, otherwise known as “statin” medications.
Clinical correlation: Hyperlipidemia is one of the most treatable risk factors of atherosclerotic vascular disease. In particular, the level of the low-density lipoprotein (LDL) correlates with the pathogenesis of atherosclerosis. Exercise, dietary adjustments, and weight loss are the initial therapy of hyperlipidemia. If these are not sufficient, then pharmacologic therapy is required. The exact LDL targets depend on the patient’s risk of cardiovascular disease. For example, if an individual has had a cardiovascular event previously (heart attack or stroke), the LDL target is 100 mg/dL; 1 to 2 risk factors without prior events = 130 mg/dL; and no risk factors = 160 mg/dL.

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**TABLE 15.5: Secondary hyperlipidemias**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Serum cholesterol</th>
<th>Serum triglyceride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Biliary obstruction</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Normal</td>
<td>Increased</td>
</tr>
</tbody>
</table>

**BOX 15.8: Clinical classification of hyperlipidemias (for treatment purpose)**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Type</th>
<th>Salient features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercholesterolemia</td>
<td>Type IIa</td>
<td>Increased LDL</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>Type I, Type IV and Type V</td>
<td>Increased VLDL, Increased IDL</td>
</tr>
<tr>
<td>Increased chylomicrons,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined hyperlipidemia</td>
<td>Type IIb and Type III</td>
<td>Increased VLDL, Increased IDL</td>
</tr>
</tbody>
</table>
Clinical Case Study 15.2 Answer

Likely diagnosis: Acute myocardial infarction.
Clinical correlation: Patient’s symptoms in this case are very typical of myocardial infarction, that is, chest pressure or chest pain, often radiating to the neck or to the left arm. The pain is usually described as deep and “squeezing chest pain.” Cardiac muscle is perfused by coronary arteries with very little redundant or shared circulation; thus, occlusion of one coronary artery usually leads to ischemia or necrosis of the corresponding cardiac muscle. Laboratory confirmation of myocardial infarction (death of cardiac muscle) includes ECG showing elevation of the ST segment and/or increase of the cardiac enzymes. When there is insufficient oxygen available for the cardiac muscle, then the glycolytic pathway must be used, which leads to a very small amount of ATP per glucose molecule.

Clinical Case Study 15.3 Answer

The patient might be suffering from familial hypercholesterolemia (FH). An LDL-C higher than 200 mg% in a patient less than 20 years is suggestive of heterozygous FH. It is an autosomal dominant condition where total cholesterol and LDL-C show severe elevation. Sometimes, it is also a moderate elevation. It carries a risk premature CAD and hence early detection and treatment are important. Exercise, dietary adjustments and weight loss are the initial steps, but if they fail drugs may be needed.

FH is due to a defect in LDL receptor. LDL receptor activity may be completely absent or up to 25% activity may be present. There are 3 types; in the first type LDL receptor is absent, in the second type there is mutation in the terminal region so that binding is affected and in the third type, there is mutation in the C terminal region so that endocytosis is affected. Cholesterol synthesis continues even when plasma cholesterol is very high in these patients.

In children with FH, typically cholesterol levels may be above 600 mg%, and LDL-C may be 200 – 400 mg%. Foam cell formation, plaque cell formation and premature CAD are typical features. Cholesterol may accumulate in other areas, leading to xanthelasmas and variety of xanthomas. Corneal arcus and valvular abnormalities are seen secondary to cholesterol deposition.

The condition may be homozygous (which is a rare condition, with an incidence of 1 in 1 million) or heterozygous (which is much more common, with an incidence of 1 in 500 persons). Men are more prone to develop CAD than women. Symptoms appear later in heterozygotes.

LEARNING POINTS, CHAPTER 15

1. LDL carries cholesterol from the liver to the heart, while HDL carries cholesterol from the heart to the liver.
2. Hypercholesterolemia is seen in diabetes mellitus, hypothyroidism, nephrotic syndrome, obstructive jaundice and in familial diseases.
3. When LDL concentration in blood increases, cholesterol gets deposited in the subintimal region of arteries.
4. Oxidized LDL (free radical damage) or glycated LDL (hyperglycemia in T2DM) have more chances of getting deposited. These modified LDL particles are taken up by macrophages. Macrophages overloaded with cholesterol are called foam cells, which form the beginning of an atherosclerotic plaque in the arterial endothelium.
5. Macrophages and platelets release lymphokines and growth factors, contributing an inflammatory component, leading to raised hsCRP level.
6. Clot formation and coronary artery thrombosis result in acute myocardial infarction.
7. Plasma total cholesterol level should be 150-200 mg/dL, and preferably below 180 mg/dL.
8. The HDL is atheroprotective cholesterol; it should be more than 40 mg/dL for men and 45 mg/dL for women. LDL-C values below 130 mg/dL are desirable. Desirable TAG level is less than 150 mg/dL.
9. Ratio between apo-B and Apo-A-I is a reliable index, ideal being 0.4.
10. Lp(a) is highly atherogenic; values above than 30 mg/dL predicting high risk.
11. Avoidable risk factors are smoking, sedentary life style and overweight. Controlling of T2DM and hypertension will also reduce the risk. Regular moderate exercise (walking for 1.5 to 2 km per day) is the basis of weight reduction.
12. Not more than 20% calories should be from fats. The fats should be proper mixtures of SFA, MUFA and PUFA.
13. Vegetable oils supply mainly omega-6 fatty acids, whereas fish is rich in atheroprotective omega-3 fatty acids. The ideal ratio of omega-6 to omega-3 in the diet is 4:1.

14. When diet control and exercise do not bring the cholesterol to desired levels, use of hypolipidemic drugs may be considered.

15. “Statins” that inhibit HMG-CoA reductase is the most common drug prescribed to lower cholesterol levels. In addition, antiplatelet agents like aspirin are also given. In persons with significant hypertriglyceridemia, fibrates may be given.

16. Abetalipoproteinemia is due to a deficiency of TAG transfer protein which interferes with the incorporation of apo-B-100 and apo-B-48 into VLDL and chylomicrons.

17. Hypoalphalipoproteinemia is due to low HDL level with high risk of CAD.

18. Tangier disease due defective efflux of cholesterol from cells occurs when ABC-A1 protein is deficient, with cholesterol ester accumulating in tissues, e.g. Orange tonsil.

19. Frederickson’s classification is based on the type of lipoprotein elevated. Six types have been described. Most common is Type IIa, which is due to defective LDL receptor, leading to decreased uptake of LDL.

20. For purposes of management, a clinical classification to 3 types is used, (a) hypercholesterolemia, (b) hypertriglyceridemia and (c) combined hyperlipidemia.

21. Hypertriglyceridemia is seen in Type I where lipoprotein lipase activity is deficient. In type IV and Type V diseases, the TAG pool is increased.

22. Combined hyperlipidemia is seen in Type IIb, where apo-B levels are high. In Type III disease, the apo-E deficiency causes defective hepatic uptake of IDL.

PART-1: ESSAY AND SHORT NOTE QUESTIONS

15-1. What is the normal cholesterol level in plasma? What is its clinical significance? What are the dietary precautions to reduce hypercholesterolemia?

SHORT NOTE QUESTIONS

15.2. HDL-cholesterol.
15.3. LDL-cholesterol.
15-5. Polyunsaturated fatty acids.

PART-2: MULTIPLE CHOICE QUESTIONS

15-1. HDL cholesterol is said to be “good” cholesterol, because
A. HDL contains enzymes to break down cholesterol
B. HDL carries cholesterol from liver to tissues where it is broken down
C. HDL carries cholesterol from tissues to liver from where cholesterol is excreted
D. HDL inhibits cholesterol synthesis

15-2. All the following statements are true with regard to type IIa hyperlipoproteinemia, except:
A. Premature atherosclerosis
B. Elevated plasma LDL cholesterol
C. Creamy layer on top of the serum
D. Xanthomata

15-3. All are true in familial hyperlipoproteinemia Type IIa, except:
15-4. Normal blood cholesterol level is:
A. 40-60 mg/100 ml
B. 70-110 mg/100 ml
C. 120-150 mg/100 ml
D. 150-200 mg/100 ml

15-5. Hypercholesterolemia is seen in the following conditions, except:
A. Diabetes mellitus
B. Thyrotoxicosis
C. Nephrotic syndrome
D. Obstructive jaundice

15-6. The characteristic finding in hypobeta-lipoproteinemia is:
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15-7. Which of the following dietary modifications have minimum hypocholesterolemic action?
A. Inclusion of fresh fruits and vegetables in diet
B. Dietary cholesterol intake less than 300mg/day
C. Intake of whole wheat bran
D. Consuming fish as the only nonvegetarian food.

15-8. Premature atherogenesis will not set in when----- is defective:
A. Cholesterol efflux regulatory protein
B. LDL receptor
C. Cholesterol ester transfer protein
D. Apolipoprotein B

15-9. Hypoalphalipoproteinemia is characteristic of
A. Fish eye disease
B. Bassen-Kornzweig syndrome
C. Floating beta disease
D. Tangier disease

15-10. A family gives a history of several members completing a century of healthy life. The cause maybe all except:
A. Sedentary lifestyle
B. Normal adipose tissue liver axis
C. Elevated HDL levels
D. Consumption of a fish based diet

ANSWERS OF MULTIPLE CHOICE QUESTIONS

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-1</td>
<td>C</td>
</tr>
<tr>
<td>15-2</td>
<td>C</td>
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<td>15-3</td>
<td>A</td>
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<td>15-14</td>
<td>A</td>
</tr>
<tr>
<td>15-15</td>
<td>C</td>
</tr>
</tbody>
</table>

15-11. Hypercholesterolemia in a 15-year-old girl may be due to the following causes, except:
A. Nephrotic syndrome
B. Hypothyroidism
C. Type IV hyperlipoproteinemia
D. Obstructive jaundice

15-12. An obese person may have all the following biochemical abnormalities, except:
A. Increased glucose tolerance
B. Hypertriglyceridemia
C. Chronic respiratory acidosis
D. High plasma insulin levels

15-13. Which of the following is the most common type of hyperlipidemia in Diabetes mellitus?
A. Elevated triglycerides with normal cholesterol
B. Normal triglycerides with elevated cholesterol
C. Elevated cholesterol and decreased triglycerides
D. Elevated cholesterol and triglycerides.

15-14. The Lipoprotein deficient in Tangier disease:
A. HDL
B. LDL
C. Lp(a)
D. IDL

15-15. Secondary hyperlipidemia occurs in all the following conditions, except:
A. Hypothyroidism
B. Alcoholism
C. Chronic pancreatitis
D. Nephrotic syndrome

PART-3: VIVA VOCE QUESTIONS AND ANSWERS

15-1. What are the salient features of hyperlipoproteinemia Type IIA?
Premature atherosclerosis; Elevated plasma LDL cholesterol; Prominent beta band on electrophoresis.

15-2. What is it due to?
Defect in LDL receptor.

15-3. Hypercholesterolemia is seen in what conditions?
Diabetes mellitus; Nephrotic syndrome; Obstructive jaundice; Hypothyroidism.

15-4. What are the important risk factors of coronary artery diseases?
Serum cholesterol level above 200 mg/dl; LDL-cholesterol level above 160 mg/dl; HDL-cholesterol level below 35 mg/dl; Lp(a) above 30 mg/dl.

15-5. What are other risk factors associated with coronary artery diseases?
Cigarette smoking, hypertension, diabetes mellitus, serum triglyceride level above 200 mg/dl; homocysteine level; sedentary life style, obesity.

15-6. What advise you will give to a person with increased cholesterol level?
Reduce cholesterol content of food; include PUFA and omega-3 fatty acids in diet; reduction of total fat intake; increase green leafy vegetables; exercise.